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Efficacy of low to moderate doses of oxcarbazepine in adult patients with newly diagnosed partial epilepsy

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ABSTRACT

Purpose: The objective of this study was to explore the efficacy of low dose of oxcarbazepine (OXC) in adult patients with newly diagnosed partial epilepsy in an actual clinical setting. The associated factors influencing the poor control of seizures were also evaluated.
Methods: The epilepsy database (2010–2014) from the Epilepsy Clinic of West China Hospital was retrospectively reviewed.
Results: A total of 102 adult patients with newly diagnosed, previously untreated partial epilepsy initially treated with OXC were included, and divided into good response group (64) and poor response group (38) according to whether they were seizure-free for at least 12 months. There were 27 (26.5%) patients becoming seizure-free with OXC 600 mg/day monotherapy. The remaining 75 patients had doses of either increasing OXC to 900 mg/day ($n = 59$) or the addition of another antiepileptic drug (AED) ($n = 16$), with another 20 (19.6%) and six (5.9%) patients becoming seizure-free, respectively ($P = 0.788$). In addition, two (2.0%) and nine (8.8%) patients became seizure-free with OXC $>$ 900 mg/day monotherapy and OXC $\geq$ 900 mg/day combination therapy, respectively. Multivariate binary logistic regression analysis revealed that the time from onset of epilepsy to treatment initiation is significantly associated with seizure control ($P = 0.02$).
Conclusion: Our results indicated that OXC at low to moderate doses is effective for the treatment of Chinese adult patients with newly diagnosed, previously untreated partial epilepsy, and a longer time interval from the onset of epilepsy to the start of treatment significantly predicts poor seizure control.

1. Introduction

Oxcarbazepine (OXC) is a second generation AED as a first-line treatment for adults and children with simple partial seizures, complex partial seizures, and partial seizures evolving to secondarily generalized seizures [1–3]. OXC is chemically related to carbamazepine (CBZ), but with a more favourable pharmacokinetic profile and improved tolerability profile [4,5]. To better manage and improve the prognosis of epilepsy, it is important to assess the treatment effects of AED accurately and formulate rational treatment plans, ideally by following outcomes from the point of treatment initiation. The efficacy and tolerability of OXC as monotherapy or adjunctive therapy, has been previously evaluated in a number of clinical trials [4,6–10]. For adults, this drug has been shown to be efficacious at a usual maintenance dose of 900–1200 mg/day and a maximum dose of 2400 mg/day as monotherapy or adjunctive therapy [4,7,9–11], but limited data are available for Chinese patients [12], and since there exists difference in race between Chinese and Occidentals, a different dose of OXC treatment in Chinese adult patients may be required. On the other hand, with strict entry and dosing criteria, regular clinical trials may fail to include practical, real world information [13,14]. Moreover, the duration of follow-up in trials is usually short, and may not be long enough to assess drug side effects [15]. Therefore, rational studies in clinical practice are increasingly recognized to provide data that further confirm and complement information derived from regulatory trials [13]. To our knowledge, for patients who are failure with the initial OXC treatment, whether increasing

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the dose of OXC is better than a second AED added is controversial and no data are available.

Therefore, we designed this retrospective study to explore the efficacy of OXC treatment in adult patients with newly diagnosed, previously untreated partial epilepsy in west China in an actual clinical setting. And the associated factors influencing the poor seizure outcome were also evaluated.

2. Methods

2.1. Patients

This was a retrospective, uncontrolled study conducted at the Epilepsy Clinic of West China Hospital, a tertiary referral centre in Chengdu, China. The epilepsy database (2010–2014) from this Epilepsy Clinic was retrospectively reviewed. The Ethics Committee of the West China Hospital, Sichuan University approved the study, and informed consent was obtained from each patient.

Patients who fulfilled the inclusion and had no exclusion criteria were consecutively included in this study. The inclusion criteria were as follows: (1) at least 16 years old and weight more than 40 kg; (2) at least two well documented, unprovoked, clinically evaluated and classified partial seizures (with or without secondary generalization) within 12 months; (3) the first AED was OXC prescribed at the epilepsy clinic at the West China Hospital, which was continued for at least 3 months; (4) no previous use of AEDs before attending our clinic; and (5) follow up by at least for 12 months. Patients were excluded from the study if they had less than one seizure per year prior to treatment. Patients with suspected partial seizures who have a clear IGE EEG were also excluded. Compliance with the treatment regimen was monitored at the clinic, and patients with persistent poor adherence to treatment, unrelated to efficacy or tolerability, seizures secondary to drug or alcohol abuse, or documented psychogenic nonepileptic seizures were also excluded.

Follow-up was started at the introduction of OXC and was ended at the discontinuation of treatment or closing date (July 2014), or death.

2.2. Treatment

For the majority of adult patients, OXC was prescribed initially as 300 mg/day for two weeks, increasing to 600 mg/day in one month. The OXC doses were adjusted as clinical circumstances dictated, with particular attention paid to efficacy and tolerability. If the patient reported intolerable adverse effects with treatment, an alternative was substituted. If the AED was well tolerated but did not completely abolish the seizures, it was continually increased to the doses or combination therapy was used, which to a large degree was consistent with previous studies [16]. However, because of the pragmatic nature of this study, there were no rigid rules concerning dose adjustments, and doses of OXC were individualized. And moreover, based on the experience of clinic practice and previous finding that Chinese patients receiving a dose of more than 900 mg/day could be more likely to develop side effects [17], and a higher risk of OXC-induced cutaneous adverse reactions [18,19], the usual maintenance dose of OXC in our patients was 600–900 mg/day and rarely more than 900 mg/day. When possible, the patients were reviewed by the same clinician every 8–12 weeks, or sooner if required. The follow-up clinical data were collected in a structured record sheet and entered into a computerized database.

2.3. Clinical information and demographic status

The following data regarding the clinical information and demographic status were obtained from the medical records and interview: age, gender, body weight, age at seizure onset, epilepsy duration, seizure type, imaging (MRI/CT) findings, previous and current AED use, time from onset of epilepsy to initiation of AED treatment, OXC treatment (initiation date, daily dose, titration regimen, date of discontinuation and reasons for discontinuation) and the occurrence of any adverse events. Previous medical history, including history of febrile seizures, cerebral infection and brain injury, and family history of epilepsy were also obtained. Duration of epilepsy was defined as the period from the seizure onset to the end of follow-up.

2.4. Statistical analysis

Data processing and analysis were performed with SPSS version 17.0 (SPSS Inc., Chicago, Illinois) for Windows. All outcome variables were summarized using descriptive statistics. Continuous variables were summarized as the mean ± SD, and categorical variables were summarized using counts and percentages. The patients were divided into two groups: those who had been seizure-free for at least 12 months were considered to have a good response (good response group) and the remaining patients (were never seizure-free for a complete year) were classified as having a poor response (poor response group). Several continuous variables were categorized. The current age was divided into 10-year groups. The median age of epilepsy onset 21 years old was selected as the cut-off point for onset age. The time from onset of epilepsy to the start of treatment was divided into 1-year groups. The two-tailed chi-square or Fisher's exact tests were used for the comparison of categorical data, whereas Student's t test or the Mann–Whitney test were used for the comparison of continuous data. Univariate binary logistic regression was performed to determine the association between the clinical and demographic variables and poor seizure outcome. A model of multivariate logistic regression analysis was constructed to determine the independent association with seizure outcome using a backwards selection of covariates, and all results were expressed as the odds ratios (ORs) and 95% confidence intervals (CIs). All P-values were two-sided, with $P < 0.05$ considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics of the included patients

A total of 102 eligible patients were included. The demographic and clinical characteristics of the included patients are summarized in Table 1. The mean age of all of the patients was 30.1 ± 12.1 years. The mean age at seizure onset was 25.6 ± 12.7 years. For the brain MRI/CT results, 82 (80.4%) were normal and the other 20 (19.6%) were abnormal. For seizure types, 28 (27.5%) patients had simple partial seizures, 22 (21.6%) had complex partial seizures and the remaining 52 (51.0%) showed partial seizures with secondary generalization. The mean age at the initiation of OXC therapy was 27.9 ± 12.0 years. The mean daily dose of OXC was 796.0 ± 185.8 mg, ranging from 600 to 1200 mg, and the time interval from onset of epilepsy to the start of treatment averaged 2.3 ± 3.3 years.

The seizure-free rates with successive regimens were shown in Fig. 1 and Table S1. Twenty-seven (26.5%) of the 102 patients achieved seizure-free with OXC 600 mg/day monotherapy. The remaining 75 patients either had daily doses of OXC increasing to 900 mg ($n = 59$) or the addition of another AED ($n = 16$), with a seizure-free rate of 33.9% (20) and 37.5% (6), respectively ($P = 0.788$) (Table S2). For the 39 patients who did not become seizure-free with OXC 900 mg/day, three were maintained on the 900 mg/day, and the remaining 36 patients either had daily doses of OXC increasing to more than 900 mg ($n = 10$) or the addition of another AED ($n = 26$), with two (20.0%) and eight (30.8%) patients becoming seizure-free, respectively. Furthermore, one of four

Table 1
Demographic and clinical characteristics of the 102 subjects included in the present study.

Variable	Good response ($n=64$)	Poor response ($n=38$)	Total ($n=102$)	P value
Gender				0.490
Male	43(67.2%)	28(73.9%)	71(69.6%)	
Female	21(32.8%)	10(26.1%)	31(30.4%)	
Age (years; mean ± SD)	30.3 ± 12.8	29.7 ± 10.8	30.1 ± 12.1	0.799
Weight (kg; mean ± SD)	61.6 ± 7.1	60.3 ± 6.3	63.1 ± 6.8	0.333
Onset age (years; mean ± SD)	26.5 ± 12.4	24.3 ± 11.3	25.6 ± 12.7	0.394
Age of therapy initiation (years; mean ± SD)	28.2 ± 12.8	27.47 ± 10.7	27.9 ± 12.0	0.764
Time from onset of epilepsy to start of treatment (years; mean ± SD)*	1.7 ± 2.7	3.4 ± 3.8	2.3 ± 3.3	0.021
Duration of epilepsy (years; mean ± SD)	3.8 ± 2.7	5.4 ± 4.9	4.4 ± 3.7	0.070
History				
Febrile seizures	2(3.1%)	4(10.5%)	6(5.9%)	0.192
Cerebral infection	2(3.1%)	5(13.2%)	7(6.9%)	0.099
Cerebral trauma	1(1.6%)	4(10.5%)	5(4.9%)	0.063
First degree relative with epilepsy	–	–	–	
Seizure type				0.236
Simple partial	21(32.8%)	7(18.4%)	28(27.5%)	
Complex partial	14(36.8%)	8(21.1%)	22(21.6%)	
Secondary GTCS	29(45.3%)	23(60.5%)	52(51.0%)	
MRI or CT results*				**0.019**
Normal	56(87.5%)	26(68.4%)	82(80.4%)	
Abnormal	8(12.5%)	12(31.6%)	20(19.6%)	
Duration of treatment (months; mean ± SD)	24.5 ± 7.9	22.2 ± 7.2	23.6 ± 7.7	0.144
Maximum dosage of OXC* (mg/day; mean ± SD)	750.0 ± 169.0	868.4 ± 191.5	796.0 ± 185.8	**0.002**
Adverse events	9(14.1%)	13(19.1%)	22(21.6%)	**0.017**

Note: The data are expressed as n (%), unless otherwise stated.
Abbreviations: SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging; GTCS, generalized tonic–clonic seizure; OXC, oxcarbazepine.
The bold in the table indicates statistically significant data.
Good response group was defined as a seizure-free remission for at least 12 months.
Poor response group was defined as no seizure-free remission for 12 months.

patients receiving a combination of OXC 1050 mg/day and an additional AED became seizure-free.

Overall, a total of 21.6% (22) of the patients reported adverse events, including dizziness ($n=6$), headache ($n=3$), drowsiness ($n=4$), nausea ($n=3$), fatigue ($n=2$), somnolence ($n=2$), weight gain ($n=1$) and hyponatraemia ($n=1$) (Table 2). All were mild to moderate in nature and the majority were transient. No skin rash was observed and no patients discontinued OXC as a result of the adverse events. Moreover, there was no significant difference in the frequency of adverse events between the patients with OXC monotherapy and those with a combination of OXC and other AEDs (16.7% vs. 28.6%, $P=0.368$) (Table 2).

3.2. Comparison of the variables in patients with good response and poor response

The patients in good response Group (64) and in poor response Group (38) did not differ significantly for gender distribution, age, weight, age at seizure onset, duration of epilepsy, age at start of therapy, duration of treatment, seizure types, history of febrile seizures, cerebral infection and cerebral trauma. However, compared to the patients with poor response, the patients with good response had a lower proportion of abnormal MRI/CT findings (12.5% vs. 31.6%, $P=0.023$) and a significantly less proportion of patients presented adverse events (14.1% vs. 19.1%, $P=0.017$), and their mean daily dose of OXC was also significantly lower than that in poor response Group (750.0 ± 169.0 mg vs. 868.4 ± 191.5 mg, $P=0.017$). Moreover, the patients with poor response had a longer time interval from the onset of epilepsy to the start of treatment (3.4 ± 3.8 vs. 1.7 ± 2.7 years, $P=0.039$) (Table 1).

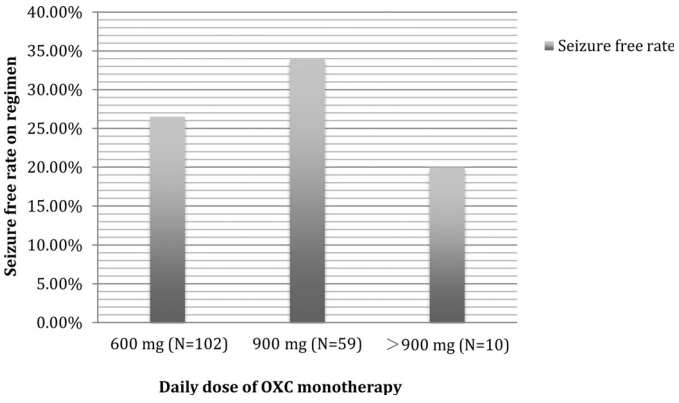

Fig. 1. Seizure-free rates with successive OXC monotherapy: 600 mg/day, 900 mg/day and more than 900 mg/day, with seizure free rate 26.5%, 33.9% and 20.0%, respectively.

3.3. Predictors related to poor response to treatment

The results of univariate binary regression showed that the longer time interval from the onset of epilepsy to the start of treatment ($P=0.041$) and abnormal brain MRI/CT findings ($P=0.023$) were associated with a poor response (details in Table S3). For the multivariable logistic regression model, only the time interval from the onset of epilepsy to the start of treatment ($P=0.020$) was independently associated with the response.

Table 2
Adverse events of the included patients.

Adverse event	Monotherapy ($n=60$)	Multi-drug ($n=42$)	Total ($n=102$)	P value
Dizziness	3(5.0%)	3(7.1%)	6(5.9%)	
Headache	2(3.3%)	1(2.4%)	3(2.9%)	
Drowsiness	2(3.3%)	2(4.8%)	4(3.9%)	
Nausea	1(1.7%)	2(4.8%)	3(2.9%)	
Fatigue	1(1.7%)	1(2.4%)	2(2.0%)	
Somnolence	1(1.7%)	1(2.4%)	2(2.0%)	
Hyponatraemia	0	1[a](2.4%)	1(1.0%)	
Weight gain	0	1(2.4%)	1(1.0%)	
Total	10(16.7%)	12(28.6%)	22(21.6%)	0.368

[a] The additional AED in the case with hyponatraemia was valproate.

Table 3
Multivariate logistic regression analyses for predictors of good outcome for newly diagnosed partial epilepsy.

Variable [a]	*B*	SEB	Odds ratio (95% CI)	*P*-value
Time from onset of epilepsy to starting treatment (years)				0.020
≤1[b]	–	–	–	
<2 and ≥1	−0.929	0.615	0.395(0.118–1.319)	0.131
<3 and ≥2	−1.721	0.735	0.179(0.042–0.756)	0.019
≥3	−1.921	0.657	0.146(0.040–0.531)	0.003

Abbreviations: *B*, beta; SEB, standard error of beta; CI, confidence interval.
[a] Age, gender, age at onset, seizure types, time from onset of epilepsy to starting treatment, febrile seizures, cerebral infection and MRI/CT results. Only significantly associated factors are listed in this table.
[b] Reference category for the odds ratio.

Furthermore, among the subgroups of the time interval, patients who had a time interval less than 1 year were more likely to become seizure-free than those who had ≥2 and <3 years interval (OR: 0.179, 95% CI: 0.042–0.756, $P = 0.019$) and ≥3 years interval (OR: 0.146, 95% CI: 0.040–0.531, $P = 0.003$) (Table 3).

4. Discussion

In the present study conducted in an actual clinical setting in west China, we found that 62.7% (64) of the 102 patients became seizure-free for at least 12 months. Further, 49 of the 64 seizure-free patients received OXC monotherapy; this confirmed that OXC is an effective first-line therapy for adult patients with newly diagnosed, previously untreated partial epilepsy [4].

As stated above, 49 (48.0%) of the patients became seizure free with OXC monotherapy, whereas several previous clinical trials evaluating the efficacy and safety of OXC monotherapy versus phenytoin [20], valproic acid [21], and CBZ [22], reported that the proportion of seizure-free patients was 55–60% for OXC, and several prospective open-label studies found a seizure-free rate of 61–63% for OXC monotherapy [23]. The slightly lower seizure-free rate for OXC monotherapy in our study may be because, in our study some patients who did not become seizure-free after OXC 600 mg/day were administered a second AED, rather than an increased dose of OXC as the patients were given in the above trials. However, a similar seizure-free rate was reported by Kwan et al. for adult patients with new onset focal or generalized seizures, of which approximately 50% of the patients become seizure-free on their first line AED [24].

For the maintenance doses of OXC, we found that compared to patients with poor response, the seizure-free patients required significantly lower doses. This was consistent with the findings from previous studies of patients who were treatment-responsive and exhibited seizure control at lower doses of the prescribed AED [16,25]. Furthermore, as expected, the average dose of OXC used in our cohort was lower than that in previous trials, which averaged approximately 1200 mg/day [4,7,8,26]. This may reflect the different dosages required for the different patient populations under evaluation. Another main finding of the present study was that an additional 20 (19.6%) patients who did not become seizure-free with OXC 600 mg/day monotherapy later became seizure-free after doses of OXC increasing to 900 mg/day. Overall, 46% (47) of our patients became seizure-free with a maintenance dose of no more than 900 mg/day of OXC monotherapy, and a few became seizure-free on OXC monotherapy at doses greater than 900 mg/day. This suggests that OXC at low to moderate doses (≤900 mg/day) are effective in treating Chinese adult patients with newly diagnosed, previously untreated partial epilepsy.

To the best of our knowledge, there is no published literature regarding whether patients would benefit more from continually increasing the dose to 900 mg/day or a second AED added to 600 mg/day, when seizures are not well controlled after the initial treatment of OXC 600 mg/day. In this retrospective study, no statistically significant differences were identified in the seizure-free rates between the two regimens. Similarly, in a randomized double-blind comparison of CBZ monotherapy (400 mg per day) versus a combination of CBZ and valproate at reduced doses (200 and 300 mg per day, respectively) conducted in patients with newly diagnosed epilepsy, no significant differences were found between the two treatments after a 1-year follow-up [27]. These above findings indicate that there are no major advantages of adjunctive therapy to monotherapy in these populations. Moreover, monotherapy for the management of epilepsy can minimize the risk of toxicity, including teratogenicity, prevent drug interactions, facilitate the assessment of drug response, and may improve patient compliance, as well as patient well-being, with the benefit of achieving full seizure control [28,29].

Here, we found that OXC was well tolerated by our patients, and all adverse events were mild to moderate in severity. No skin rash was reported in our cohort. This was likely because that we included patients taking OXC for at least 3 months, which may have excluded patients who reported a rash and then substituted another AED for OXC, and it may also be related to the low initiation dosage of OXC and the slow titration in our patients. Although there was a trend towards adverse reported among the patients on combination therapy, the difference was not statistically significant. This finding was similar to a randomized study, in which monotherapy and polytherapy were compared in previously untreated patients [27]. We found that patients who became seizure-free reported a significantly less proportion of adverse events than those with a poor response. The main reason for this difference may be that the majority of patients who were seizure-free took significantly lower doses that those who were not seizure-free, and more patients who were seizure-free took monotherapy than those who were not seizure-free.

It is important to identified patients whose seizures are likely to be pharmacoresistant early on, which allows them to be referred for epilepsy surgery at the most appropriate juncture [30]. Previously published studies showed a significant effect for seizure types, aetiology, age of onset, duration of epilepsy, number of seizures before starting AED treatment, history of febrile convulsions and the response to the first AED on prognosis [31–34]. In the present study, we found that only longer time interval from onset of epilepsy to the start of AED treatment significantly indicated poor response. It may be related to that patient with longer duration of pre-treatment seizures usually had experienced more seizures before the beginning of AED treatment. This finding was in accordance with the view that a long history and high numbers of pre-treatment seizures were thought to correlate with a poor outcome, and early treatment of seizures, thereby minimizing the number of subsequent seizures, was considered key to preventing the emergence of drug-resistant epilepsy [35,36]. As previous studies have shown, repeated seizures could produce neuronal loss and mossy fibre sprouting in the hippocampus, which in turn can reinforce their production forming excitatory recurrent circuits, and then resulting in drug resistance [37,38].

Because this was a single-centre study, it had good consistency for the evaluation methodology, data collection, and data analysis. However, our study also has several limitations. The primary limitation is the small number of patients studied. We only included patients continuing on OXC for a minimum of three months and did not take retention on OXC treatment into consideration. This may diminish the value of data on safety in this study. In addition, no data was showed that the number of

seizure or seizure density was not involved in response. This may result in the weakness of the conclusion about the effect of delay treatment. Because this was a retrospective study, some of the epilepsy information may have been affected by recall bias. However, this may be controlled for by performing population-based studies or multicentre studies in the future. Despite these limitations, we believe that our study has useful applications in everyday clinical practice.

5. Conclusion

OXC at low to moderate dose is effective for the treatment of Chinese adult patients with newly diagnosed, previously untreated partial epilepsy, without introducing significant adverse events. A longer time interval from the onset of epilepsy to the start of treatment significantly predicts the poor seizure control, and treating patients early may lead to improved outcomes.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2015.03.019.

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